

**Clinical trial results:****A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Assess the Safety, Tolerability, Pharmacokinetics and Efficacy of NBI-827104 in Subjects with Essential Tremor****Summary**

EudraCT number	2020-006012-24
Trial protocol	NL
Global end of trial date	13 June 2022

Results information

Result version number	v1 (current)
This version publication date	24 June 2023
First version publication date	24 June 2023

Trial information**Trial identification**

Sponsor protocol code	NBI-827104-ET2016
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04880616
WHO universal trial number (UTN)	-
Other trial identifiers	Toetsingonline number: NL76780.056.21, Sponsor internal number: NBI-827104-ET2016

Notes:

Sponsors

Sponsor organisation name	Neurocrine Biosciences
Sponsor organisation address	12780 El Camino Real, San Diego, United States, 92130
Public contact	Neurocrine Medical Information, Neurocrine Biosciences, +1 877-641-3461, medinfo@neurocrine.com
Scientific contact	Neurocrine Medical Information, Neurocrine Biosciences, +1 877-641-3461, medinfo@neurocrine.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 June 2022
Global end of trial reached?	Yes
Global end of trial date	13 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objectives of the trial were to evaluate the efficacy, safety, and tolerability of NBI-827104 in participants with essential tremor (ET).

Protection of trial subjects:

The study was conducted in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines and with the laws and regulations of the country in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 31
Worldwide total number of subjects	31
EEA total number of subjects	31

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were randomized (1:1) to 1 of 2 treatment sequences - Treatment Sequence 1: NBI-827104-Placebo or Treatment Sequence 2: Placebo-NBI-827104.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment Sequence 1: NBI-827104-Placebo

Arm description:

Participants received NBI-827104 for 28 days in treatment period 1 and placebo for 28 days in treatment period 2. There was a 14-day washout period between treatments.

Arm type	Experimental
Investigational medicinal product name	NBI-827104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

NBI-827104 was administered per schedule specified in the arm description.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to NBI-827104 was administered per schedule specified in the arm description.

Arm title	Treatment Sequence 2: Placebo-NBI-827104
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Arm description:

Participants received placebo for 28 days in treatment period 1 and NBI-827104 for 28 days in treatment period 2. There was a 14-day washout period between treatments.

Arm type	Experimental
Investigational medicinal product name	NBI-827104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

NBI-827104 was administered per schedule specified in the arm description.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo matched to NBI-827104 was administered per schedule specified in the arm description.

Number of subjects in period 1	Treatment Sequence 1: NBI-827104- Placebo	Treatment Sequence 2: Placebo-NBI- 827104
Started	16	15
Received at least 1 dose of study drug	16	15
Completed	14	14
Not completed	2	1
Adverse event	1	1
Withdrawal by Subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment Sequence 1: NBI-827104-Placebo
Reporting group description: Participants received NBI-827104 for 28 days in treatment period 1 and placebo for 28 days in treatment period 2. There was a 14-day washout period between treatments.	
Reporting group title	Treatment Sequence 2: Placebo-NBI-827104
Reporting group description: Participants received placebo for 28 days in treatment period 1 and NBI-827104 for 28 days in treatment period 2. There was a 14-day washout period between treatments.	

Reporting group values	Treatment Sequence 1: NBI-827104-Placebo	Treatment Sequence 2: Placebo-NBI-827104	Total
Number of subjects	16	15	31
Age categorical Units: Subjects			
Adults (18-64 years)	8	8	16
From 65-84 years	8	7	15
Age continuous Units: years			
arithmetic mean	56.4	60.0	
standard deviation	± 18.2	± 11.9	-
Gender categorical Units: Subjects			
Female	2	6	8
Male	14	9	23

End points

End points reporting groups

Reporting group title	Treatment Sequence 1: NBI-827104-Placebo
Reporting group description: Participants received NBI-827104 for 28 days in treatment period 1 and placebo for 28 days in treatment period 2. There was a 14-day washout period between treatments.	
Reporting group title	Treatment Sequence 2: Placebo-NBI-827104
Reporting group description: Participants received placebo for 28 days in treatment period 1 and NBI-827104 for 28 days in treatment period 2. There was a 14-day washout period between treatments.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description: Participants received placebo for 28 days in either treatment period 1 or 2.	
Subject analysis set title	NBI-827104
Subject analysis set type	Full analysis
Subject analysis set description: Participants received NBI-827104 for 28 days in either treatment period 1 or 2.	

Primary: Change from Baseline to Day 28 of Each Treatment Period in Amplitude at Peak Frequency of Postural Tremor in the More Severely Affected Hand (Log Base 10 Scale), Measured Using Laboratory Tremography

End point title	Change from Baseline to Day 28 of Each Treatment Period in Amplitude at Peak Frequency of Postural Tremor in the More Severely Affected Hand (Log Base 10 Scale), Measured Using Laboratory Tremography
End point description: Tremor amplitude at peak frequency of postural tremor (extended hand position) in the more severely affected hand was measured using laboratory tremography. Tremography was performed using an accelerometer attached to the participant's hand. Least square (LS) mean and standard error (SE) was calculated using the mixed-effects model for repeated measures. Full analysis set included all randomized participants who had at least 1 dose of study treatment and at least 1 postbaseline assessment for the primary efficacy variable. Overall number of participants analyzed = participants evaluable for this endpoint.	
End point type	Primary
End point timeframe: Baseline, Day 28 of each treatment period	

End point values	Placebo	NBI-827104		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	30	30		
Units: milligrams square (mg ²)/hertz (Hz)				
least squares mean (standard error)	-0.29 (± 0.12)	-0.32 (± 0.12)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Actual number of participants analyzed = 30	
Comparison groups	Placebo v NBI-827104
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7805
Method	Mixed models analysis

Secondary: Change from Baseline in Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale (PS) Total Score (Independent Blinded Video Rating) at Day 28 of Each Treatment Period

End point title	Change from Baseline in Essential Tremor Rating Assessment Scale (TETRAS) Performance Subscale (PS) Total Score (Independent Blinded Video Rating) at Day 28 of Each Treatment Period
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End point description:

TETRAS -PS was used to assess essential tremor as scored by the independent video raters. TETRAS-PS quantified tremor in the head, face, voice, limbs, and trunk. The overall subscale total score ranges from a minimum of 0 to a maximum of 64. A lower score indicated improvement and a better outcome. LS mean and SE calculated using mixed-effects model for repeated measures. Full analysis set: all randomized participants who had at least 1 dose of study treatment and at least 1 postbaseline assessment for primary efficacy variable. Overall number of participants analyzed=participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Baseline, Day 28 of each treatment period

End point values	Placebo	NBI-827104		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	29		
Units: units on a scale				
least squares mean (standard error)	-0.87 (± 0.77)	-1.94 (± 0.75)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in TETRAS Activities of Daily Living (ADL) Total Score at Day 28 of Each Treatment Period

End point title	Change from Baseline in TETRAS Activities of Daily Living (ADL) Total Score at Day 28 of Each Treatment Period
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End point description:

TETRAS ADL subscale has 12 items that assess speech, occupational impairment, social impact, and activities affected primarily by upper limb tremor. Each item was rated on a scale of 0 (no impact of tremor) to 4 (severe impact). The sum of the individual scores provided an overall total score, which

ranges from a minimum of 0 to a maximum of 48. A lower score indicated improvement and a better outcome. LS mean and SE was calculated using the mixed-effects model for repeated measures. Full analysis set included all randomized participants who had at least 1 dose of study treatment and at least 1 postbaseline assessment for primary efficacy variable. Overall number of participants analyzed = participants evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
Baseline, Day 28 of each treatment period	

End point values	Placebo	NBI-827104		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	30		
Units: units on a scale				
least squares mean (standard error)	-1.10 (± 0.87)	-2.97 (± 0.82)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression of Change (CGI-C) Score

End point title	Clinical Global Impression of Change (CGI-C) Score
End point description:	
<p>The CGI-C is a 7-point scale that rated the overall global improvement since the initiation of study drug dosing, ranging from 1 (very much improved) to 7 (very much worse), as assessed by the clinician. Lower scores indicated better quality of life. LS mean and SE was calculated using the mixed-effects model for repeated measures. Full analysis set included all randomized participants who had at least 1 dose of study treatment and at least 1 postbaseline assessment for primary efficacy variable. Overall number of participants analyzed = participants evaluable for this endpoint.</p>	
End point type	Secondary
End point timeframe:	
Day 28 of each treatment period	

End point values	Placebo	NBI-827104		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28	29		
Units: units on a scale				
least squares mean (standard error)	3.61 (± 0.16)	3.43 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 (after dosing) up to Day 84

Adverse event reporting additional description:

Safety analysis set included all randomized participants who had at least 1 dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Participants received placebo for 28 days in either treatment period 1 or 2.

Reporting group title	NBI-827104
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Reporting group description:

Participants received NBI-827104 for 28 days in either treatment period 1 or 2.

Serious adverse events	Placebo	NBI-827104	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	NBI-827104	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 30 (70.00%)	24 / 30 (80.00%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	14	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	19	
Orthostatic hypotension			

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 13	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	5	16	
Nervous system disorders			
Disturbance in attention			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	11	45	
Dizziness			
subjects affected / exposed	4 / 30 (13.33%)	11 / 30 (36.67%)	
occurrences (all)	37	154	
Dizziness postural			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	5	
Essential tremor			
subjects affected / exposed	3 / 30 (10.00%)	6 / 30 (20.00%)	
occurrences (all)	26	40	
Headache			
subjects affected / exposed	13 / 30 (43.33%)	9 / 30 (30.00%)	
occurrences (all)	76	40	
Paraesthesia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	46	
Presyncope			
subjects affected / exposed	1 / 30 (3.33%)	2 / 30 (6.67%)	
occurrences (all)	47	26	
Somnolence			
subjects affected / exposed	1 / 30 (3.33%)	6 / 30 (20.00%)	
occurrences (all)	1	69	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	12	
Fatigue			

subjects affected / exposed occurrences (all)	5 / 30 (16.67%) 39	5 / 30 (16.67%) 87	
Injection site haematoma subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 5	1 / 30 (3.33%) 9	
Eye disorders Dry eye subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 30	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 8	1 / 30 (3.33%) 5	
Dry mouth subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 6	4 / 30 (13.33%) 23	
Nausea subjects affected / exposed occurrences (all)	4 / 30 (13.33%) 22	1 / 30 (3.33%) 10	
Psychiatric disorders Euphoric mood subjects affected / exposed occurrences (all)	1 / 30 (3.33%) 2	2 / 30 (6.67%) 27	
Insomnia subjects affected / exposed occurrences (all)	3 / 30 (10.00%) 25	1 / 30 (3.33%) 3	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 30 (6.67%) 28	0 / 30 (0.00%) 0	
Myalgia subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	2 / 30 (6.67%) 13	
Infections and infestations COVID-19			

subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	
occurrences (all)	13	24	
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	3 / 30 (10.00%)	
occurrences (all)	8	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2021	<ul style="list-style-type: none">• Changed the observation period post in-clinic dosing.• Added an extra overnight stay to collect a pharmacokinetic (PK) sample.• Updated instructions for digital spiral analysis per the study center's standard operating procedure.• Added duplicate baseline measurements for resting-state electroencephalogram and digital spiral analysis.• Added duplicate tremography measurements at baseline and each postbaseline timepoint.
13 August 2021	<ul style="list-style-type: none">• Clarified that stable use of medication that might produce tremor or interfere with the evaluation of tremor could be continued if the Principal Investigator agreed that stable use of the medication was not the cause of the tremor or influenced the tremor intensity.• Removed restrictions regarding the timing of in-clinic meals other than breakfast.• Removed restriction around timing of the ophthalmic exam during the screening period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported